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The Effect of Chalcogen–Chalcogen Bond Formation in the New Delhi Metallo-β-Lactamase 1 Enzyme to Counteract Antibiotic Resistance

Antibiotics resistance is rapidly becoming an important needing of nowadays society, due to the inefficiency of many widely adopted drugs, such as penicillins and carbapenems. This takes place because a number of bacteria involved in the onset of severe human's diseases, like Escherichia coli, Klebsiella pneumoniae, Acinetobacter, Pseudomonas aeruginosa, and Enterobacter cloacae, have developed defensive enzymatic response to the antibiotic's activity. Among these enzymes, there is the New Delhi metallo-β-lactamase 1 (NDM-1) that can efficiently hydrolyze β-lactam containing compounds. NDM-1's knockout is therefore of interest for new therapies that inhibit the enzyme selectively, to avoid the chemical alteration of antibiotic. Promising results of NDM-1 inhibition have been recently obtained in presence of ebselen (EbSe), a molecule with wide range of already-known beneficial for human health. The enzyme has resulted indeed inhibited and, more intriguingly, its Zn2 cation of the active site pocket is removed. The mechanism remains poorly understood and it is therefore of high interest to acquire detailed understanding of it. Aiming to contribute to such needing topic, the current presentation concerns an in-depth computational investigation on the interaction between NDM-1 and EbSe, based on density functional theory calculations and μs-molecular dynamics simulations. [1] The reaction mechanism is elucidated employing large quantum chemical cluster active site model and considering different mechanistic proposals. It is unveiled that Cys208 of Zn2's coordination sphere attacks the Se atom of the ligand, favoured by proton donation of active site Lys211. The effect of chalcogen atom is further investigated considering the ebsulfur, where Se is replaced by S atom. Extensive molecular dynamics simulations allowed to detect the consequences of the covalent-bond formation to the inhibition from both structural and energetic point of view. The role of active site L3 and L10 loop and the energetic feasibility of Zn2 expulsion have been highlighted, thus providing a complete scenario on the activity of the enzyme. [1]
[1] G. Ciardullo, M. Prejanò, A. Parise, N. Russo, T. Marino, J. Chem. Theory Comput. 2025, 21, 1422–1431

Primary author(s) : Dr. PREJANÒ, Mario (Università della Calabria); Dr. CIARDULLO, Giada; Dr. PARISE, Angela; Prof. RUSSO, Nino; Prof. MARINO, Tiziana

Presenter(s) : Dr. PREJANÒ, Mario (Università della Calabria)